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(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **GAVIN, Brian, Charles** [IE/IE]; GlaxoSmithKline, P.O. Box 700, Grange Road, Rathfarnham, 16 Dublin (IE).

(74) Agent: **LEAROYD, Stephanie, Anne**; GlaxoSmithKline, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

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(54) Title: MEDICAL COMPOSITIONS COMPRISING (R,R)-FORMOTEROL AND ROFLEPONIDE

(57) Abstract: The present invention is concerned with pharmaceutical formulations comprising a combination of (R,R)-formoterol and rofleponide and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.



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MEDICAL COMPOSITIONS COMPRISING (R,R)-FORMOTEROL UND ROFLEPONIDE

The present invention is concerned with combinations of (R,R)-formoterol and rofleponide, particularly compositions containing a combination of (R,R)-formoterol and rofleponide and the use of such compositions in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

Formoterol, i.e. 2'-hydroxy-5'-[(RS)-1-hydroxy-2{[(RS)-p-methoxy- α -methylphenethyl]amino}ethyl]formanilide, particularly its fumarate salt is a well-known adrenoreceptor agonist which is now used clinically in the treatment of bronchial asthma and related disorders. Formoterol includes two asymmetric centres and in a particular form exists as the (R,R)- isomer. The (R,R) isomer of formoterol has been described previously, for example, in WO98/21175 and US5795564.

WO 92/13872 describes rofleponide i.e. 16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione, salts and esters thereof and pharmaceutical formulations thereof. Rofleponide is an antiinflammatory corticosteroid, which is proposed for use in the treatment of bronchial asthma and related disorders.

WO 99/00134 describes combinations of formoterol and rofleponide but is silent as to the utility of (R,R)-formoterol.

Although formoterol fumarate and rofleponide may be effective therapies, there exists a clinical need for asthma therapies having potent and selective action and having an advantageous profile of action.

Therefore, according to the present invention there is provided a combination of (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same or different pharmaceutical formulations or sequentially. If there is sequential administration, the delay in administering the second compound should not be such as to lose the beneficial therapeutic effect of the combination.

According to a further aspect of the present invention, there is provided a pharmaceutical formulation comprising (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients. According to a preferred aspect of the present invention, there is provided a pharmaceutical formulation comprising (R,R)-formoterol fumarate and rofleponide palmitate, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients. In the most preferred aspect, the above pharmaceutical formulations are suitable for administration by inhalation.

It is to be understood that the present invention covers all combinations of particular and preferred aspects of the invention described herein.

As would be appreciated by the skilled person, rofleponide contains several asymmetric centres. The present invention includes each isomer of rofleponide, particularly the (22R) and (22S) isomers, either in substantially pure form or admixed in any proportions. The isomers of rofleponide have been described previously in WO 92/13872.

By the term "physiologically functional derivative" is meant a chemical derivative of (R,R)-formoterol or rofleponide having the same physiological function as the free compound, for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids. Pharmaceutically acceptable acid addition salts include but

are not limited to those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic, isethionic, and naphthalenecarboxylic, such as 1-hydroxy-2-naphthalenecarboxylic acids.

Pharmaceutically acceptable esters of (R,R)-formoterol or rofleponide may have a hydroxyl group converted to a C₁₋₆alkyl, aryl, aryl C₁₋₆ alkyl, or amino acid ester.

As mentioned above, both (R,R)-formoterol and rofleponide and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have been described for use in the treatment of respiratory diseases. Therefore, formulations of (R,R)-formoterol and rofleponide and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2 -adrenoreceptor agonist and/or an antiinflammatory corticosteroid is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration of a therapeutically effective amount of a combination of (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. The present invention further provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative

thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient. In a preferred aspect, there is provided such a method which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising (R,R)-formoterol fumarate and rofleponide palmitate, and a pharmaceutically acceptable carrier or excipient. In particular, the present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

In the alternative, there is provided a combination of (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, for use in therapy, particularly for use in the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated. In particular, there is provided a pharmaceutical formulation comprising (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (suitably, (R,R)-formoterol fumarate) and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (suitably, rofleponide palmitate), and a pharmaceutically acceptable carrier or excipient for use in therapy, particularly for use in the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated. In a preferred aspect, the invention is concerned with the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

The amount of (R,R)-formoterol and rofleponide, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. As a monotherapy, (R,R)-formoterol

fumarate is generally administered to adult humans by aerosol inhalation at a dose of 12mcg or 24mcg twice daily. As a monotherapy, rofleponide is described in WO 92/13872 as being administered to adult humans by aerosol inhalation at a dose of from 10mcg to 1000mcg, preferably 20mcg to 250mcg.

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While it is possible for the active ingredients of the combination to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. When the individual compounds of the combination are administered separately, they are generally each presented as a pharmaceutical formulation as described previously in the art.

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Pharmaceutical formulations are often prescribed to the patient in "patient packs" containing the whole course of treatment in a single package. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions and, therefore, lead generally to more successful treatment. It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each component compound, and containing a package insert instructing the patient to the correct use of the invention is a desirable additional feature of the invention.

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Hereinafter, the term "active ingredients" means (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, preferably (R,R)-formoterol fumarate, and rofleponide, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, preferably rofleponide palmitate.

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Suitably, the pharmaceutical formulations which are suitable for inhalation according to the invention comprise the active ingredients in amounts such that each actuation provides therapeutically effective dose, for example, a dose of (R,R)-formoterol of 10mcg to 150mcg, preferably 24mcg and a dose of rofleponide of 10mcg to 1.6mg, preferably 20mcg to 250mcg.

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The pharmaceutical formulations according to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists), or other β_2 -adrenoreceptor agonists (such as salbutamol, salmeterol, fenoterol or terbutaline and salts thereof), or anticholinergic agents (such as ipratropium, or tiotropium).

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), intranasal, inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredients into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations for inhalation include powder compositions which will preferably contain lactose, and spray compositions which may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluoroethane, carbon dioxide or other suitable gas. Suitable aerosol formulations include those described in EP 0372777 and WO93/11743. For suspension aerosols, the active ingredients should be micronised so as to permit inhalation of substantially all of the active ingredients

into the lungs upon administration of the aerosol formulation, thus the active ingredients will have a particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 1 to 10 microns, for example, 1 to 5 microns.

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Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

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Capsules and cartridges or for example gelatin, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator may be formulated containing a powder mix of the active ingredients and a suitable powder base such as lactose or starch. In this aspect, the active ingredients are suitably micronised so as to permit inhalation of substantially all of the active ingredients into the lungs upon administration of the dry powder formulation, thus the active ingredients will have a particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 1 to 10 microns.

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Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

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Preferred unit dosage formulations are those containing a pharmaceutically effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient. Thus, in the case of formulations designed for delivery by metered dose pressurised aerosols, one actuation of the aerosol may deliver half of the therapeutically effective amount such that two actuations are necessary to deliver the therapeutically effective dose.

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It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question. Furthermore, the claimed formulations include bioequivalents as defined by the US Food and Drugs Agency.

For a better understanding of the invention, the following Examples are given by way of illustration.

5 EXAMPLES

A: Metered Dose Inhalers

Example 1

| | Per actuation |
|---------------------------|---------------|
| (R,R)-formoterol fumarate | 24 microgram |
| Rofleponide | 200 microgram |
| 1,1,1,2-Tetrafluoroethane | to 75.0mg |

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The micronised active ingredients are weighed into an aluminium can, 1,1,1,2-tetrafluoroethane is then added from a vacuum flask and a metering valve is crimped into place.

15 Similar methods may be used for the formulation of Example 2:

Example 2

| | Per actuation |
|---------------------------|---------------|
| (R,R)-formoterol fumarate | 12 microgram |
| Rofleponide | 100 microgram |
| 1,1,1,2-Tetrafluoroethane | to 75.0mg |

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B: Dry Powder Inhalers

Example 3

| | Per cartridge or blister |
|---------------------------|---------------------------|
| (R,R)-formoterol fumarate | 24 microgram |
| Rofleponide | 200 microgram |
| Lactose Ph. Eur. | to 12.5mg or to 25.0mg |

- 5 The active ingredients are micronised and bulk blended with the lactose in the proportions given above. The blend is filled into hard gelatin capsules or cartridges or in specifically constructed double foil blister packs to be administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being a Trademark of Glaxo Group Limited).

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Similar methods may be used for the formulations of Example 4:

Example 4

| | Per cartridge or blister |
|---------------------------|---------------------------|
| (R,R)-Formoterol fumarate | 12 microgram |
| Rofleponide | 100 microgram |
| Lactose Ph. Eur. | to 12.5mg or to 25.0mg |

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Claims

1. A pharmaceutical formulation comprising (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.
2. A pharmaceutical formulation comprising (R,R)-formoterol fumarate and rofleponide palmitate, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.
3. A pharmaceutical formulation according to claim 1 or claim 2 which comprises another corticosteroid, another β_2 -adrenoreceptor agonist or an anticholinergic agent.
4. A pharmaceutical formulation according to claim 3, wherein the other β_2 -adrenoreceptor agonist is salbutamol, salmeterol, fenoterol, terbutaline, or a salt thereof.
5. A pharmaceutical formulation according to claim 3 wherein the anticholinergic agent is ipratropium or tiotropium.
6. A pharmaceutical formulation according to any one of claims 1 to 6 which is suitable for administration by inhalation.
7. A pharmaceutical formulation according to any one of claims 1 to 6 which is suitable for intranasal administration.
8. A pharmaceutical formulation consisting of (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and optionally one or more other therapeutic ingredients, and 1,1,1,2 - tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane or mixtures thereof as propellant.

9. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist and/or an antiinflammatory corticosteroid is indicated, which comprises
5 administration of a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 9.
10. A method according to claim 11 wherein the clinical condition is a disease
10 associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/GB 01/01629

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/575 A61K31/167 A61P11/06 //(A61K31/575,31:167)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO 99 00134 A (ASTRA AB) 7 January 1999 (1999-01-07) | 1-10 |
| Y | claims 1-17 | 1-10 |
| Y | WO 98 21175 A (SEPRACOR INC) 22 May 1998 (1998-05-22) cited in the application claims 19-21 | 1-10 |
| Y | US 5 795 564 A (MORLEY JOHN ET AL) 18 August 1998 (1998-08-18) cited in the application abstract | 1-10 |
| Y | WO 92 13872 A (ASTRA AB) 20 August 1992 (1992-08-20) cited in the application claims 1-11 | 1-10 |
| | --- -/-- | |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| Y | O'CONNOR B J: "COMBINATION THERAPY" PULMONARY PHARMACOLOGY AND THERAPEUTICS, ACADEMIC PRESS, NEW YORK, NY, US, vol. 11, no. 5/6, 1998, pages 397-399, XP000911059 ISSN: 1094-5539 the whole document ---- | 1-10 |
| Y | BOWLER S: "LONG ACTING BETA AGONISTS" AUSTRALIAN FAMILY PHYSICIAN, XX, XX, vol. 27, no. 12, December 1998 (1998-12), pages 1115,1117-1118, XP000973076 the whole document ----- | 1-10 |

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/GB 01/01629

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|---|---|---------------------|----------------------------|------|---------------------|
| WO 9900134 | A | 07-01-1999 | AU 8135098 | A | 19-01-1999 |
| | | | BR 9810452 | A | 05-09-2000 |
| | | | EE 9900594 | A | 15-08-2000 |
| | | | EP 1009408 | A | 21-06-2000 |
| | | | HU 0002533 | A | 28-12-2000 |
| | | | NO 996438 | A | 28-02-2000 |
| | | | PL 337722 | A | 28-08-2000 |
| | | | SK 184799 | A | 12-06-2000 |
| | | | TR 9903272 | T | 21-08-2000 |
| WO 9821175 | A | 22-05-1998 | AU 722859 | B | 10-08-2000 |
| | | | AU 5175598 | A | 03-06-1998 |
| | | | EP 0938467 | A | 01-09-1999 |
| | | | US 6040344 | A | 21-03-2000 |
| US 5795564 | A | 18-08-1998 | US 6068833 | A | 30-05-2000 |
| WO 9213872 | A | 20-08-1992 | AP 366 | A | 21-10-1994 |
| | | | AT 178611 | T | 15-04-1999 |
| | | | AU 661471 | B | 27-07-1995 |
| | | | AU 1230792 | A | 07-09-1992 |
| | | | BG 62211 | B | 31-05-1999 |
| | | | BG 97971 | A | 25-04-1994 |
| | | | CA 2103924 | A | 05-08-1992 |
| | | | CN 1064079 | A, B | 02-09-1992 |
| | | | CN 1140178 | A, B | 15-01-1997 |
| | | | CN 1140059 | A, B | 15-01-1997 |
| | | | CZ 9301496 | A | 16-03-1994 |
| | | | DE 69228870 | D | 12-05-1999 |
| | | | DE 69228870 | T | 19-08-1999 |
| | | | DK 570454 | T | 18-10-1999 |
| | | | EE 3111 | B | 15-04-1996 |
| | | | EP 0570454 | A | 24-11-1993 |
| | | | ES 2133315 | T | 16-09-1999 |
| | | | FI 933450 | A | 03-08-1993 |
| | | | GR 3030657 | T | 29-10-1999 |
| | | | HK 1010733 | A | 24-03-2000 |
| | | | HU 64973 | A, B | 28-03-1994 |
| | | | IE 920166 | A | 12-08-1992 |
| | | | IL 100532 | A | 14-05-1996 |
| | | | JP 6505232 | T | 16-06-1994 |
| | | | KR 216720 | B | 01-10-1999 |
| | | | MX 9200324 | A | 01-09-1992 |
| | | | NO 304073 | B | 19-10-1998 |
| | | | NZ 241210 | A | 26-08-1993 |
| | | | PL 170000 | B | 31-10-1996 |
| | | | PT 100086 | A, B | 31-05-1994 |
| | | | RO 111195 | B | 30-07-1996 |
| | | | RU 2111212 | C | 20-05-1998 |
| | | | SG 52557 | A | 28-09-1998 |
| | | | SI 9210065 | A | 28-02-1995 |
| | | | SK 79693 | A | 09-03-1994 |
| | | | US 5674861 | A | 07-10-1997 |
| | | | US 5939409 | A | 17-08-1999 |
| | | | ZA 9200233 | A | 28-10-1992 |